IN THE CLAIMS:

Please amend claim 31 as follows:

Claim 31, line 5, before "nitric," insert --topically applied--,

line 6, before "nitric," insert --topically applied--.

REMARKS

I. Status of the Claims

Claims 31-38, 40-54, and 56-66 remain pending in this application. Claim 31 has been amended to more distinctly point out that which Applicant believes to be the invention. Support for the amendment can be found in the specification as originally filed, for example, at page 3, lines 19-26. Accordingly, no issue of new matter is raised by this Amendment.

II. Rejection Under 35 U.S.C. § 103(a)

Claims 31-38, 40-54, and 56-66 have been rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 5,716,625 (Hahn) in view of U.S. Patent No. 5,358,969 (Williamson). Applicant respectfully traverses this rejection.

In order to show a *prima facie* case of obviousness, three factors must be established. The U.S. Patent and Trademark Office ("the Office") must demonstrate that there is some suggestion or motivation, either in the references themselves or in

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the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine references' teachings in the manner suggested by the Office. *See* M.P.E.P. § 2143. Additionally, the Office must show that there is a reasonable expectation of success in the proposed modification. *Id.* Finally, the prior art references must teach or suggest all claim limitations. *Id.* If the Office does not show that all of these criteria have been met, the Office has not met its burden, and *prima facie* obviousness has not been established. Applicant submits that neither of the first two factors have been established, and thus, the rejection under 35 U.S.C. § 103(a) is improper and should be withdrawn.

A. There is no Suggestion in the References or in the Knowledge of Those of Ordinary Skill in the Art That Would Motivate the Skilled Artisan to Modify the References as Proposed by the Office

According to the Office, "the motivation to combine the teachings of Hahn and Williamson comes from the theory of Hahn, and accordingly, it would have been obvious for one of an ordinary skill in the art to incorporate NO synthase inhibitors in a pharmaceutical or cosmetic composition, with an expectation to inhibit any irritation and associated inflammation caused by the substances." *See* final Office Action, page 2, line 18 to page 3, line 3. The Office's underlying basis for this assertion is the teaching in Hahn "of combining a substance that can cause irritation with an anti-irritant in the

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same composition." *See* outstanding final Office Action, page 2, lines 11-13. Applicant disagrees.

Simply because a reference or references can be modified or combined does not render the modification or combination obvious. *See In re Gordon*, 733 F.2d 900, 902, 221 U.S.P.Q. 1125, 1127 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification."). The motivation to modify the prior art must flow from some teaching in the art that suggests the desirability or incentive to make the modification needed to arrive at the claimed invention. *See In re Napier*, 55 F.3d 610, 613, 34 U.S.P.Q.2d 1782, 1784 (Fed. Cir. 1995) ("Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination."). It is impermissible for the Office to use hindsight after viewing Applicant's disclosure as a blueprint to reconstruct the claimed invention from isolated pieces of the prior art, as this contravenes the statutory mandate of section 103 of judging obviousness at the point in time when the invention was made. *See Grain Processing Corp. v. American Maize-Prods. Co.*, 840 F.2d 902, 907, 5 U.S.P.Q.2d 1788, 1792 (Fed. Cir. 1988).

As the Office acknowledges, Hahn teaches topical formulations comprising an anti-irritant amount of aqueous soluble strontium (II) cation, which may optionally also contain an irritant, and methods for using the same to inhibit skin irritation. *See, e.g.*,

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abstract and column 10, lines 43-47. However, this can hardly be said to provide motivation to formulate all compositions containing an irritant and any anti-irritant. Rather, the Office must show motivation to make the particular composition containing an irritant and an anti-irritant (or at least the class of anti-irritants) which it considers obvious.

In the present case, the Office has failed to adequately point out why it would be obvious to modify the strontium (II) cation containing compositions of Hahn by substituting the metal cation with the NO synthase inhibitors of Williamson (*i.e.*, aminoguanidine, N,N'-diaminoguanidine, methylguanidine, or 1,1'-dimethylguanidine). The Office has provided no evidence that one of ordinary skill in the art would expect the particular metal cation of Hahn and the particular guanidines of Williamson to be interchangeable in the composition of Hahn. And, as discussed below, that even if such a substitution were made, that one of ordinary skill in the art would expect success. In fact, since these two components are not from the same class of chemicals or even remotely related, one of ordinary skill in the art would not expect that they are interchangeable. Simply because the two might have a similar result does not support a finding of obviousness of the proposed substitution.

Further, the Office has not pointed to any suggestion in the references themselves that would motivate one of ordinary skill in the art to make the proposed modification, other than to rely on the broad "theory" disclosed by Hahn of the combination of irritant and anti-irritant in the same composition. However, this broad

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"theory" does not establish the desirability of the particular modification proposed, as required by the MPEP under current Federal Circuit case law. Rather, it is Applicant's position that the only motivation that would suggest the modification proposed by the Office derives from Applicant's disclosure, which, as the Office knows, is improper. Thus, the Office has not met its burden of establishing motivation sufficient to support a finding of *prima facie* obviousness.

B. There is no Reasonable Expectation that the Modification Proposed by the Office will be Successful

Beyond looking to the prior art to determine if it suggests doing what the inventor has done, one must also consider if the art provides the required expectation of succeeding in that endeavor. MPEP § 2143; *In re Dow Chem.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988) ("Both the suggestion and the expectation of success must be founded in the prior art, not in applicant's disclosure."). "Obviousness does not require *absolute* predictability, but a reasonable expectation of success is necessary." *In re Clinton*, 527 F.2d 1226, 1228, 188 U.S.P.Q. 365, 367 (C.C.P.A. 1976).

The Office has not shown that one of ordinary skill in the art would reasonably expect that the modification proposed by the Office would be successful. On the contrary, the skilled artisan would believe, based on the teachings of Hahn and Williamson, that the proposed modification would be unsuccessful. The compositions

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according to Hahn are topical compositions,[1] in which the strontium (II) cation is applied directly to the skin to reduce irritation associated with topically applied skin irritants. *See, e.g.,* column 9, line 59 to column 10, line 10. Williamson, on the other hand, discloses oral, intraveneous, intraperitoneal, or subcutaneous administration (i.e., systemic treatment rather than direct application) of the particular guanidines useful according to the invention. *See, e.g.*, Examples of Williamson. There is no reasonable expectation that the systemically therapeutic guanidines of Williamson would be successful as a topical anti-irritant, nor has the Office pointed to any as it must to satisfy its burden of establishing obviousness.

On the contrary, Hahn teaches that the effect of any particular agent on nerve activity and sensation in intact human bodies is very difficult to predict. *See* Column 6, lines 55-58. Further, Hahn teaches that different agents will affect human tissue differently, depending on such considerations as mode of administration, among others. *See* Column 7, lines 2-8. Likewise, Hahn discloses that the same agent can have widely varying affect on the human body depending on the method of administration. *See* Column 7, lines 9-23 (Magnesium, which is known to have a depressant effect on nerves, surprisingly produces neither anesthesia nor analgesia when administered

[1] Although Applicant recognizes that Hahn teaches a topical oral formulation for treating sore throat and other oral pain and irritation at column 16, lines 40-58, it is clear from the entire disclosure of the reference that the method by which the oral or throat pain and irritation is treated is topical, and in the same manner as the remainder of the treatments according to the invention disclosed therein (i.e., treatment by contact with the composition). It is therefore distinct from the oral formulations according to Williamson, which are ingested orally for the purpose of systemic treatment.

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intraveneously, and instead produces paralysis of the skeletal muscles. But when administered orally magnesium does not produce paralysis or depressed neural activity. When administered in direct contact with the brain, magnesium results in depressed neural or synaptic activity, and induces a sleep-like state).

Thus, taking into account the explicit teaching of Hahn regarding the unpredictability of different agents, one of ordinary skill in the art would have no expectation that the guanidines of Williamson would function as in the same manner and give similar results as strontium (II) cations. Indeed, one of ordinary skill in the art could expect that the guanidines of Williamson may very well affect nerve activity and sensation in a different way than strontium (II) cations. In addition, based on the teachings of Hahn that the mode of administration may change the efficacy of the anti-irritant, one of ordinary skill in the art would not expect success in a topical composition containing the NO synthase inhibitors of Williamson, since Williamson teaches systemic administration of the particular guanidines useful for the invention.

Accordingly, one of ordinary skill in the art would have no reasonable expectation of success in a topical composition containing NO synthase inhibitors, based on the disclosures of Hahn and Williamson. Thus, the Office has not met its burden pursuant to MPEP § 2143 to establish a reasonable expectation of success sufficient to support a finding of *prima facie* obviousness.

In light of the above amendments and remarks, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

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III. Conclusion

In view of the foregoing remarks, Applicant respectfully requests prompt reconsideration and timely allowance of the pending claims.

If there are any other fees due in connection with this filing, please charge the fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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